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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
SHEN, WU CHENG WINSTON	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,410	MARTUZA ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,18-20 and 28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,18-20 and 28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/26/2009 and 08/26/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 07/20/2009 has been entered.

Claims 1-15, 17, and 21-27 are cancelled. No claim is amended. Claims 16, 18-20 and 28-32 are pending and currently under examination.

This application 10/788,410 file don 03/01/2004 is a DIV of 09/625,509, filed on 07/25/2000, now PAT 6,699,468, which is a DIV of 09/004,511, filed on 01/08/1998, now PAT 6,139,834, which is a CON of 08/478,800, filed on 06/07/1995 ABN, which is a CON of 08/264,581, filed on 06/23/1994, now PAT 5,585,096 (changes are in bold for emphasis). The series of parent applications of instant application listed above is based on the Application Data Sheet filed on 08/06/2007.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 16, 28, and 29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Roizman et al.** (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of **Vile et al.** (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994). Applicant's arguments filed 07/20/2009 have been fully considered and they are not persuasive.

Previous rejection is ***maintained*** for the reasons of record advanced on pages 11-14 of the office action mailed on 02/14/2008, and pages 4-14 of the office action mailed on 03/18/2009.

For clarity and completeness of this office action, the reasons of record advanced on pages 6-13 of the office action mailed on 08/18/2008 and pages 4-14 of the office action mailed on 03/18/2009 is reiterated below.

Claim 16 filed on 07/20/2009 reads as follows: A herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell, and (ii) an alteration in the γ34.5 gene such that no functional γ34.5 gene product is made, wherein the neurovirulence of said herpes simplex virus is attenuated.

Claim interpretation: The limitation "capable of eliciting an immune response against a tumor cell" recited in amended claim 16 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Roizman et al. teaches the following: **(i)** Novel modified HSV vectors for gene therapy (See abstract, Roizman et al., 2001), which reads on the limitation "an expressible non-herpes simplex virus nucleotide sequence" recited in claim 16 of instant applicant application, **(ii)** The function of the gene γ34.5 in its ability to enable the virus to replicate, multiply and spread in the central nervous system (CNS) was demonstrated by a set of recombinant viruses and by testing their abilities to cause fatal encephalitis in the mouse brain. The mutant viruses lacking the gene therefore lost their ability to multiply and spread in the CNS and eyes and therefore are non-

pathogenic. See Chou et al., Science, 250: 1212-1266, 1990 (See lines 35-42, col. 4, Roizman et al., 2001), **(iii)** The use of the HSV-1 virus with a null mutation in the γ34.5 gene provides a method of therapeutic treatment of tumorogenic diseases both in the CNS and in all other parts of the body. The "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread. Therefore, given the ability to target tumors within the CNS, the γ34.5 minus virus has proven a powerful therapeutic agent for hitherto virtually untreatable forms of CNS cancer (See bridging paragraph, col. 5-6, Roizman et al., 2001). Roizman et al. further teaches that the γ34.5 gene placed under a suitable target specific promoter in the context of treating a tumor cell (which reads on the limitation of claim 28 of instant application) would be expressed, thus inducing an anti-apoptotic effect in the neuron without the potential for stress induced neurovirulence (See lines 44-46, 56-60 col. 6, Roizman et al., 2001), and **(iv)** The embodiment of the present invention describes a method which involves combining ICP34.5 (i.e. γ34.5) or a biological functional equivalent thereof with a pharmaceutically acceptable carrier in order to form a pharmaceutical composition, which reads on claim 29 of instant application.

Roizman et al., do not teach do not teach a herpes simplex virus with a genome that expresses an exogenous cytokine gene recited in claim 16.

Vile et al. teaches that **(i)** transduction of tumor cells *in vitro* with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity when such cells are returned *in vivo* to syngeneic animals (See first sentence of Introduction, page S59, Vile et al., 1994), **(ii)** constitutively producing cytokines such as IL-2, IL-4, and GM-CSF could be use as "cancer vaccine" by activation of immune system (See

conclusions, right column, second paragraph, Vile et al., 1994), and **(iii)** use of the 5' flanking region of the murine tyrosinase gene directs expression of three different cytokine genes murine interleukin 2 (IL-2), IL-4 and macrophage colony-stimulating factor (M-CSF) specifically to murine melanoma cells (See abstract, Vile et al. *Ann Oncol.* 5 Suppl 4:59-65, 1994).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Roizman et al. (2001) regarding the characteristics of a mutant herpes simplex virus comprising a disrupted γ34.5 gene of herpes simplex virus, which is non-pathogenic and has lost the ability of to multiply and spread in the CNS and in all other parts of the body, with the teachings of Vile et al. (1994) regarding exogenous expression of a cytokine gene results in diminishment or elimination of tumorigenicity of tumor cells via elicitation of immune response, to arrive at the claimed HSV with disrupted both γ34.5 that exhibits no neurovirulence, and expressing a cytokine gene that elicit an immune response against a tumor cell, as recited in claims 16, 28, and 29 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Roizman et al. with the teachings of Vile et al. (1994) because (i) the γ34.5 gene mutation would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, column 5), and (ii) the exogenous expression of a cytokine gene would result in diminishing or eliminating tumorigenicity of tumor cells, as taught by Vile et al.

There would have been a reasonable expectation of success given (1) the demonstration that the "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, (2) the

demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's Arguments and ***Responses to Applicant's Arguments***

It is noted that Applicant's arguments filed on 07/20/2009 are presented in a collective manner directed to all three maintained 103 rejections.

(A) Applicant argues that there was a disincentive to have combined prior-art teachings in the manner posited by the examiner, which defeats the alleged *prima facie* case under Section 103. Applicant argues that one of ordinary skill in the art would not have combined the design parameters of (a) long-lasting expression of a transgene for gene-therapy purposes and (b) killing host cells by means of a replicating virus, since these parameters were understood to serve conflicting objectives. Applicant argues that, thus, expression of a cytokine requires an intact target cell, while oncolytic therapy by the mutant HSV destroys the target cell. See response filed on December 18, 2008, at page 6. Applicant argues that it necessarily follows that the prior art would not have led one of ordinary skill to modify either Roizman or Roizman/Chang to arrive at the claimed invention (See pages 4-5 of Applicant's arguments file don 07/20/2009).

In response, the Examiner's response the Applicant's arguments filed on December 18, 2008, at page 6 has been elaborated and documented on pages 10-12 of the office action mailed on 03/18/2009. For the clarity of record of this office action, the response documented on pages 10-12 of the office action mailed on 03/18/2009 is reiterated below.

Applicant's arguments based on the asserted deficiency of Vile et al has been fully considered and found not persuasive because the *prima facia* obvious rejection is based on the combined teachings of Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001) in view of Vile et al. (*Ann Oncol.* 5 Suppl 4:59-65, 1994), rather than based on anyone of the two individual references alone. Vile et al. is relied on for the teachings regarding the recited limitation "an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine". Applicant is reminded that, as stated in the maintained rejection under *Claim interpretation*: The limitation "capable of eliciting an immune response against a tumor cell" recited in claim 16 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any. Furthermore, claim 16 is a product claim, a HSV with null mutation of γ34.5 gene and a cytokine gene inserted in the HSV genome. Whether the expression of a cytokine alone can lead to a statistically significant reduction in tumor growth, as discussed by Vile et al., is not required by the claimed product. Related to this discussion, as stated in the maintained rejection, Vile et al. teaches that transduction of tumor cells *in vitro* with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity when such cells are returned *in vivo* to syngeneic animals (See first sentence of Introduction, page S59, Vile et al., 1994). Furthermore, as disclosed by Vile et al., the goal of cancer gene therapy is to target specifically to cancer cells, and Vile et al. teaches using tumor-specific promoter to overcome non-tumor cell specific expression of gene of interest. Bearing the goal of targeting specifically to cancer cells, Chang et al. [See below, the rejection of claims18-20 under 35 U.S.C. 103(a)] teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) grows in actively dividing cells (e.g. cancer cells), but the growth is severely impaired in growth

arrested, non-dividing cells (See bridging paragraph, pages 437-438, Chang et al., 1991). Chang et al. further teaches that the introduction of *a foreign gene* (e.g. a cytokine gene taught by Vile et al.) into neuronal cells by a RR-negative herpes simplex virus, and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons (See abstract, Chang et al., 1991). Therefore, a skilled person in the art would certainly be motivated to incorporate the teachings of Vile et al., and Chang et al. in the context of non-pathogenic HSV taught by primary reference Roizman to arrive at the claimed the HSV with recited genome in claim 16 of instant application.

Moreover, Applicant's arguments that one of ordinary skill the art would not have combined the design parameters of (a) long-lasting expression of a transgene for gene-therapy purposes and (b) killing host cells by means of a replicating virus, since these parameters were understood to serve conflicting objectives, have been fully considered and found not persuasive. It is noted that the context of gene therapy taught by Vile et al. is for treating malignant melanoma by expressing a cytokine (IL-2, IL-4, and M-CSF) driven by a tumor specific promoter from a plasmid. There is no contradiction for the goal of gene therapy of cancer treatment taught by Vile et al. to ultimately kill cancer cells without harming normal cells by oncolytic virus taught by Roizman et al. and by Chang et al. Furthermore, using and developing various viral vectors, including HSV, for gene therapy purposes are common for the artisan in the filed of gene therapy.

(B) Applicant argues that the evidence of record warrants withdrawal of the rejection. Applicant states that evidencing the art-recognized incongruity of parameters (a) and (b), supra,

the Rabkin Declaration of record attests to the fact that, at the time of filing, the conventional wisdom in the field included an expectation that cytokines would protect a host from HSV infection and prevent HSV replication in the host. In particular, see Exhibits A, C, F, and H that accompany the Rabkin Declaration. The claimed invention, which requires that a cytokine-expressing HSV infect and replicate in tumor cells, thus contravenes what the skilled artisan would have done and expected before the present invention was made. Applicant states that Examiner Shen's maintenance of the rejection to date seems focused on his weighing of the declaration evidence, also discussed above. In particular, Applicant argues that the Examiner has been inclined to discount the attestations of Declarant Rabkin, an expert in the HSV field, largely on the strength of the Examiner's impression that cytokine is expressed only after a herpes simplex virus of the invention has infected a host cell and, hence, that such expression could not protect the cell from HSV infection. Applicant states that, as a matter of law, however, this impression should not outweigh the declarant's averment regarding the state of the relevant art prior to the claimed invention (see below). As a matter of fact, moreover, Applicant argues that the Examiner's impression is not well-conceived because, as was pointed out during the July 9th interview, the oncolytic effects of the claimed invention require that the mutant HSV not only infect a tumor cell but also continue to replicate in that cell and others cells of the tumor. This latter functionality is precisely that which the skilled artisan would have expected cytokine expression to impair. See the Rabkin Declaration, e.g., at paragraph 4. Applicant states, in this context, Examiner Shen noted during the interview that the exhibits accompanying the Rabkin Declaration were articles showing a protective effect for a cytokine that was not expressed from an HSV. Accordingly, the examiner "encourage[d] Applicants to provide evidence(s) supporting

that expression of a cytokine gene from an HSV indeed blocks the HSV replication." Interview Summary, continuation sheet. Applicant states that, to address this point, Applicants presently submit a post-filing publication by Ghiasi et al., J. Virology 76:9369-78 (2002) (Exhibit 1 to this response), which reports that expression of cytokine IL-2 by HSV results in decreased virus replication, both in vitro and in vivo. See the abstract of the Ghiasi article, as well as the text from page 9072 in the left column, second full paragraph; through page 9073 in the left column, and Figures 3 and 4 (See pages 5-7 of Applicant's arguments file don 07/20/2009).

In response, the Examiner's response the Applicant's arguments regarding the asserted incongruity of parameters (a) and (b), has been addressed in the response **(A)**. Examiner's Response to Exhibits A, C, F, and H that accompany the Rabkin Declaration have been elaborated and documented on pages 14-16 of the office action mailed on 03/18/2009. For the clarity of record of this office action, the response documented on pages 13-14 of the office action mailed on 03/18/2009 is reiterated below.

Applicant's arguments pertaining to the Declaration by inventor Rabkin, attesting that those in the field would not have considered it obvious to express cytokines in the HSV, has been addressed on pages 14-15 of the Final office action mailed 08/18/2008. In short, the Declaration by inventor Rabkin focuses on the effect of endogenously expressed cytokine in elicitation of protective immunity, however, in the claimed HSV, a cytokine gene would not be expressed until after the HSV vector infected targeted cells. Furthermore, as elaborated below, the efficacy of the claimed HSV in cancer gene therapy is the intended use of the claimed HSV.

The Examiner notes that it is not uncommon that expression of a protein (cytokine, in this case) may result in multiple effects. For instance, expression of cytokine endogenously has been

reported to elicit protective immunity under normal physiological conditions (the essence of Declaration by inventor Rabkin) and expression of exogenous cytokine in cancer cells leads to activation of immune system which in turn eliminate cancer cells (reported by Vile et al. cited in this 103 rejection).

The Examiner acknowledges that the intended use for cancer gene therapy of the HSV recited in the claims of instant application may function in multiple possible scenarios, including (A) to (C) discussed by Applicant. The Examiner also acknowledges that even as of current status of art, the outcome of cancer gene therapy in general remains unpredictable and needs to be evaluated on a case-by-case basis. However, it is worth emphasizing, again, the claims of instant application is directed to a product, not a method of using said product in cancer gene therapy that results a statistically significant reduction in tumor growth, as Applicant argues. In this regard, as stated in the response under **(A)** section, claim 16 is a product claim, a HSV with null mutation of ribonucleotide reductase and a cytokine gene inserted in the HSV genome. The structure and inherent properties of the structure of claimed HSV as a whole was clearly *prima facie* obvious based on the combined teachings of Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001) in view of Vile et al. (*Ann Oncol.* 5 Suppl 4:59-65, 1994). The efficacy of the claimed HSV in cancer gene therapy is the intended use of the claimed HSV, which the Examiner agree with Applicant that the intended use of the claimed HSV in treating a given cancer remains unpredictable, as Applicant argues that several possible scenarios may occur. Nevertheless, a skilled person in the art would be motivated to make the claimed HSV based on the combined references and to test how effective the claimed HSV may be in cancer gene therapy.

It is worth noting that none of declaratory evidence provided in Exhibits A, C, F, and H that accompany the Rabkin Declaration is commensurate in scope with the claimed HSV products --- i.e. a HSV with null mutation of both γ34.5 and ribonucleotide reductase and a cytokine gene inserted in the HSV genome. Similarly, the newly provided reference Ghiasi et al. (2002) teaches the use of HSV to express IL-2 under LAT promoter (i.e. promoter for late gene expression) in the context of evaluation of replication and virulence the HSV that does not comprise the γ34.5 mutation, which renders the HSV non-pathogenic, and ribonucleotide reductase mutation, which render HSV replicates in dividing cancer cells but not in non-dividing cells. Ghiasi et al. (2002) showed that (i) IL-2 appears to protect against ocular HSV infection, as HSV-IL-2 proved to be less virulent than either the wild-type virus or its marker-rescued virus (the survival of mice coinfected with the parental virus and HSV-IL-2 was higher than that of mice infected with the parental virus alone, and depletion of IL-2 resulted in increased virulence of HSV-IL-2) and (ii) the ability of IL-2 to protect against ocular HSV-1 infection appears to be related to the activity of both the CD4+ and CD8+ T-cell populations, as depletion of either type of T cell resulted in a higher mortality rate upon HSV-IL-2 infection (See left column, page 9070, Ghiasi et al.). However, the data presented by Ghiasi et al. (2002) do not provide any relevant information regarding claimed HSV expressing a cytokine from a HSV that comprises both γ34.5 mutation and ribonucleotide reductase mutation because the claimed HSV are already non-pathogenic/virulent due to the presence of γ34.5 mutation, even in the absence of the effect of IL-2 expression from LAT promoter in the HSV taught by Ghiasi et al. Therefore, there is no asserted disincentive for any skilled artisan to combine the teachings of Roizman et al. with the teachings of Vile et al. (1994), especially in light of the teachings by Vile et al. that transduction

of tumor cells *in vitro* with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity when such cells are returned *in vivo* to syngeneic animals (See first sentence of Introduction, page S59, Vile et al., 1994). Furthermore, Vile et al teaches that expression of IL-2 in the murine melanoma cells completely abrogated their tumorgenicity in syngeneic mice (See right column, summary, page S59) and loss of tumorgenicity correlates with continued IL-2 expression (see right column, page 62), the skilled artisan would have reasonable expected that the expression of IL-2 from a viral vector, such as claimed HSV, would enhance the anti-tumor effects of the virus. Applicant is also reminded that the fact that applicant may have recognized another characteristic and/or advantage of claimed product (e.g. reducing tumor growth) which would flow naturally from following the suggestion of the prior art (i.e. Roizman et al. and Vile et al. in this case) cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

With regard to Applicant's arguments that Examiner's position that cytokine gene cloned in the claimed HSV would only be expressed after the HSV has infected cells is "not well-conceived", the Examiner notes that a virus, by definition, can only become a living entity inside a host cell. In other words, a virus cannot become alive and actively express a gene in the absence of host cellular machinery. Therefore, contrary to Applicant's assertion that the cytokine gene cloned in the claimed HSV would only be expressed after the HSV has infected cells is Examiner's "impression", the Examiner's position in this regard, is based on the fundamental knowledge and well accepted definition of what a virus is. Furthermore, Applicant appeared to

agree with the Examiner's position pertaining to cytokine gene cloned in the claimed HSV would only be expressed after the HSV has infected cells, otherwise it would have been meaningless for Applicant to argue three possible scenarios (A) to (C) (See page 12 of office action mailed on 03/18/2009) regarding how the timing of cytokine gene expression may affect oncolytic activity of claimed HSV.

(C) Applicant argues that in light of this last consideration and the additional citation to Ghiasi et al. (2002), as requested by the examiner, applicants submit that the evidence of record, including the Rabkin Declaration, amply substantiates the patentability of the claimed invention over any permutation of teachings properly gleaned from the cited prior art. Thus, Applicant argues that no rebuttal of the alleged prima facie case under Section 103 is either necessary or warranted. Applicant argues that to gauge what would have been unexpected in this regard; applicants note that the Vile publication actually reports an elevation in cytokine expression without an accompanying change in tumor growth. Thus, Vile et al. state: No statistically significant reduction in tumor growth was seen following injection of any of these cytokine expression plasmids either alone or in combination at the dose tried. However, using RT-PCR to monitor levels of cytokine mRNA, all three cDNAs were expressed in vivo up to 16 days after the single DNA injection ....Page 62, in the right column, at lines 9-14.

Applicant argues that a post-filing publication by Liu et al., *Cancer Res.* 65:1532-40 (2005) (present Exhibit 2), demonstrates that an HSV vector expressing IL-12 is significantly better at inhibiting tumor growth than the HSV vector alone. More specifically, Liu shows that the treatment by "NV1042" the IL-12-expressing HSV vector, significantly increased survival

rate (Figure 1A) and decreased the tumor size (Figure 1 B) relative to treatment by "NV1023" the HSV vector sans cytokine expression. With nothing in Vile or the primary reference(s) that is suggestive of this disparity in results, the skilled artisan necessarily would have deemed the demonstrated enhancement in rumor-growth inhibition, per Liu, to be an unexpected result (or "synergy") achieved with applicants' claimed invention.

In response, the Examiner emphasizes again, Applicant's arguments based on the asserted deficiency of Vile et al has been fully considered and found not persuasive because the *prima facia* obvious rejection is based on the combined teachings of Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001) in view of Vile et al. (*Ann Oncol.* 5 Suppl 4:59-65, 1994), rather than based on anyone of the two individual references alone. Vile et al. is relied on for the teachings regarding the recited limitation "an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine". Applicant is reminded that, as stated in the maintained rejection under *Claim interpretation*: The limitation "capable of eliciting an immune response against a tumor cell" recited in claim 16 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any. Furthermore, claim 16 is a product claim not a method claim, i.e. a HSV with null mutation of γ34.5 and a cytokine gene inserted in the HSV genome. The patentability of claimed products relies on the structures of the products, not the intended use of the products by the Applicants. Whether the expression of a cytokine alone can lead to a statistically significant reduction in tumor growth, which is one of the intended uses of the product, as discussed by Vile et al., is not required by the claimed product. In this regard, it is worth noting again, Vile et al. teaches that transduction of tumor cells *in vitro* with cDNA encoding various cytokines and/or immune accessory molecules has been shown to diminish or

eliminate tumorigenicity when such cells are returned *in vivo* to syngeneic animals (See first sentence of Introduction, page S59, Vile et al., 1994). Furthermore, Vile et al teaches that expression of IL-2 in the murine melanoma cells completely abrogated their tumorgenicity in syngeneic mice (See right column, summary, page S59) and loss of tumorgenicity correlates with continued IL-2 expression (see right column, page 62), the skilled artisan would have reasonable expected that the expression of IL-2 from a viral vector, such as claimed HSV, would enhance the anti-tumor effects of the virus, by diminishing or eliminating tumorigenicity of tumor cells reported by Vile et al.

With regard to the teachings by Liu et al., *Cancer Res.* 65:1532-40 (2005) (present Exhibit 2), demonstrating that an HSV vector expressing IL-12 is significantly better at inhibiting tumor growth than the "NV1042" HSV vector alone, which Applicant asserted as unexpected (synergistic) result, the Examiner notes that "NV1042" HSV vector is not commensurate in scope with the claimed HSV products because the "NV1042" HSV vector taught by Liu et al. comprise deletion in ICP47 gene. Moreover, nowhere in the teachings by Liu et al. indicates any greater than additive or unexpected effect when IL-12 is expressed from the "NV1042" HSV vector as compared to the effect of IL-12 and the effect of NV1042" HSV individually. Furthermore, disclosure of a post-filing art being consistent with Applicant's intended use of claimed product does not constitute unexpected results. It is also noted that any evidence of unexpected results must be commensurate in scope with the claimed invention, and that a greater, or greater than additive, effect is not necessarily sufficient to overcome a *prima facie* case of obviousness because such an effect can either be expected or unexpected MPEP 716.02 (a) and (d). "Expected beneficial results are evidence of obviousness of a claimed

invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967); *Ex parte Blanc*, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989). Even if the results of Liu et al. were to be considered as unexpected as Applicant asserted, it is further noted that the teachings of IL-12 is not commensurate in scope with the claimed HSV products --- i.e. any cytokine expressed from a HSV with null mutation of both γ34.5 and ribonucleotide reductase. In this regard, the asserted unexpected results of IL-12 taught by Liu et al., based on the unexpected nature, cannot be extrapolated to any other cytokine. Consistent with this rationale, **Varghese et al.** teaches enhanced therapeutic efficacy of IL-12, but not GM-CSF, expressing oncolytic herpes simplex virus for transgenic mouse derived prostate cancers using the same series of HSV vector reported by Liu et al. (2005) (See title and abstract, Varghese et al., Enhanced therapeutic efficacy of IL-12, but not GM-CSF, expressing oncolytic herpes simplex virus for transgenic mouse derived prostate cancers, *Cancer Gene Ther.* 13(3):253-65, 2006). Therefore, taken together as discussed in this paragraph, the asserted unexpected results based on the post-filing art by Liu et al. (2005) cannot overcome the *prima facie* obvious case based on the combined teachings of Roizman et al. in view of Vile et al.

2. Claims 18-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Roizman et al.** (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of **Vile et al.** (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994) as applied to claims 16, 28, and 29 above, and further in view of **Chang et al.** (Chang et al., A

gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, *Virology*, 185(1):437-40, 1991). Applicant's arguments filed 12/18/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 14-17 of the office action mailed on 02/14/2008, and pages 14-18 of the office action mailed on 03/18/2009.

For clarity and completeness of this office action, the reasons of record advanced on pages 14-17 of the office action mailed on 08/18/2008 and pages 14-18 of the office action mailed on 03/18/2009 is reiterated below.

Claim interpretation: The limitation "capable of eliciting an immune response against a tumor cell" recited in amended claim 16 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any. It is noted that in the art G207, as recited in claim 20 of instant application, is the name of an HSV that contains deletions of both copies of the gamma34.5 gene as well as a LacZ insertion in the ICP6 gene, which is the large subunit (ICP6) of ribonucleotide reductase (RR).

The teachings of Roizman et al. and Vile et al. have been discussed in the preceding rejection of claims 16, 28, and 29 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. 2001 in view of Vile et al., 1994.

However, the combined teachings of Roizman et al. and Vile et al., do not teach a herpes simplex virus with a genome that comprises alteration in the ribonucleotide reductase (RR) gene (recited in claim 19 of instant application).

At the time of filing of instant application, a herpes simplex virus with a genome that is altered in the ribonucleotide reductase gene was known in the art. For instance, Chang et al. teaches that herpes simplex virus type-1 (HSV-1) is able to infect both non-neuronal and

neuronal cells (See introduction, Chang et al., 1991). Chang et al. also teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) is a useful vector for gene delivery into neuronal cells. Chang et al. used hrR3, a genetically engineered HSV-1 mutant which has an in-frame insertion of the bacterial LacZ gene into the HSV gene that encodes the large subunit (ICP6) of ribonucleotide reductase (RR), resulting in the ICP6::lacZ chimeric gene. Chang et al reported that the infection was performed in the presence of acyclovir; hrR3 appeared to become "latent". Chang et al. further teaches that the introduction of *a foreign gene* (e.g. a cytokine gene taught by Vile et al.) into neuronal cells by a RR-negative herpes simplex virus, and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons (See abstract, Chang et al., 1991). Chang et al further teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) grows in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells (See bridging paragraph, pages 437-438, Chang et al., 1991).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine (i) the characteristics of a mutant herpes simplex virus comprising an nucleotide sequence encoding a cytokine, a disrupted γ34.5 herpes simplex, which is non-pathogenic and has lost the ability of to multiply and spread in the CNS and in all other parts of the body, as taught by combined teachings of Roizman et al. 2001 and Vile et al., 1994, with (ii) the characteristics of a RR-negative herpes simplex virus that can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, as taught by Chang et al. 1991.

It would have been obvious at the time of filing to combine the teachings of Roizman et al. 2001, and Vile et al., 1994, with the teachings of Chang et al. 1991, to arrive at the claimed herpes simplex viruses as recited in claims 18-20 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Roizman et al. 2001, Vile et al., 1994, with the teachings of Chang et al. 1991 because the disrupted γ34.5 gene renders the HSV vector non-pathogenic and the disrupted ribonucleotide reductase gene render the HSV vector specific targeting to fast dividing tumor cells without harming healthy cells, for the treatment of CNS or non-CNS cancers. Combination of the mutations would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, column 5), that targets specifically fast dividing tumor cells, as taught by Chang et al., 1991, which indicates the disruption of ICP6, either by LacZ insertion in the ICP6:LacZ strain or by deletion in the ICP6Δ strain, results in severe growth impairment in non-dividing cells (See first paragraph, left column, page 438).

There would have been a reasonable expectation of success given (1) the demonstration that the "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, (2) the demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994, and (3) the demonstration that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) vector for introduction of a foreign gene can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, by the teachings of Chang et al., 1991.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's Arguments and ***Responses to Applicant's Arguments*** are the same as discussed in the preceding rejection of claims 16, 28, and 29 as being unpatentable over Roizman et al. in view of Vile et al. Furthermore, regarding the motivation to combine the cited reference, it is worth adding that, bearing the goal of targeting specifically to cancer cells taught by Roizman et al. and Vile et al., Chang et al. teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) grows in actively dividing cells (e.g. cancer cells), but the growth is severely impaired in growth arrested, non-dividing cells (See bridging paragraph, pages 437-438, Chang et al., 1991). Chang et al. further teaches that the introduction of *a foreign gene* (e.g. a cytokine gene taught by Vile et al.) into neuronal cells by a RR-negative herpes simplex virus, and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons (See abstract, Chang et al., 1991).

3. Claim 30-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Roizman et al.** (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) in view of **Vile et al.** (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994) as applied to claim 16, 28, and 29 above, and further in view of **McKay et al.** (WO 92/14821, publication date 09/03/1992, PCT/US92/01375, priority date 02/22/1991), and **Wright, Jr.** (US 5,639,656, issued Jun. 17, 1997, filed 03/31/1994). Applicant's arguments filed 12/18/2008 have

been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 17-20 of the office action mailed on 02/14/2008 and pages 18-22 of the office action mailed on 03/18/2009.

For clarity and completeness of this office action, the reasons of record advanced on pages 18-22 of the office action mailed on 08/18/2008 and pages 18-22 of the office action mailed on 03/18/2009 is reiterated below.

Claim interpretation: The limitation "capable of eliciting an immune response against a tumor cell" recited in amended claim 16 is considered as inherent properties of recited cytokine, and thereby given limited patentable weight, if any.

The teachings of Roizman et al. and Vile et al. have been discussed in the preceding rejection of claims 16, 28, and 29 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. 2001 in view of Vile et al., 1994.

However, the combined teachings of Roizman et al. and Vile et al., do not teach a herpes simplex virus with a genome that expresses a exogenous cytokine gene, wherein an essential viral gene product of said virus is under the control of a tumor cell-specific promoter rather than its own promoter, wherein said promoter being nestin promoter, basic fibroblast growth factor (bFGF) promoter, or epidermal growth factor (EGF) promoter, as recited in claims 30-32 of instant application.

At the time of filing of instant application, it was known in the art that the expression of certain growth factor genes including bFGF, EGF, nestin genes can serve as markers for detection of various cancers, indicating the promoters of these growth factors being tumor specific with respect to its regulation. For instance, McKay et al. teaches that nestin expression

as an indicator of neuroepithelial brain tumors, indicating the nestin promoter being tumor specific with respect to its regulation (See title and abstract, WO 92/14821, publication date 09/03/1992). Wright, Jr. 1997 teaches the expression of bFGF, EGF can be used as biological markers of prostate cancer (CaP) or benign prostate hyperplasia (BPH) (See title and lines 30-36. column 2, Wright et al., 1997). Furthermore, as indicated before, Roizman et al. further teaches that the γ34.5 gene placed under a suitable target specific promoter in the context of treating a tumor cell (which reads on claim 28 of instant application) would be expressed, thus inducing an anti-apoptotic effect in the neuron without the potential for stress induced neurovirulence (See lines 44-46, 56-60 col. 6, Roizman et al., 2001). Accordingly, it would have been *prima facie* obvious the nestin promoter, bFGF promoter, EGF promoter are tumor cell specific promoters, and thereby can be used for expressing an essential viral gene as recited in claims 30-32 of instant application by the combined teachings of Roizman et al., 2001, Vile et al., McKay et al., 1991, and Wright, 1997.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to exogenously express a nucleotide sequences encoding a cytokine, whose transduction of tumor cells with cDNAs encoding various cytokines has been shown to diminish or eliminate tumorigenicity in syngeneic animals, in a γ34.5 defective HSV vector, as taught by the combined teachings of Roizman et al., 2001 and Vile et al., 1994, and to have an essential viral gene product under the control of a tumor cell-specific promoter of nestin or bFGF, or EGF, as taught by the teachings of Wright or McKay et al., in the said herpes simplex virus vector with disrupted both γ34.5 and expressing nucleotide sequences encoding a

cytokine, to ensure that the said HSV vector exhibits no neurovirulence to non-cancer cells, by the combined teachings of Roizman et al. 2001 and Vile 1994.

It would have been obvious at the time of filing to combine (i) the teachings of Roizman et al. 2001, and Vile et al., 1994, regarding a HSV vector for cancer treatment with the expression of a nucleotide sequences encoding a cytokine from a HSV vector, wherein as essential viral gene product placed under a suitable target specific promoter, with (ii) the teachings by Wright or McKay et al., regarding gene product being under the control of the tumor specific promoters of nestin or bFGF, or EGF to arrive at the claimed herpes simplex viruses as recited in claims 30-32 of instant application.

One having ordinary skill in the art would have been motivated to utilize the HSV vector that exhibits characteristics favorable gene transfer, expresses nucleotide sequence encoding a cytokine, and infects specifically to tumor cells, by combined teachings of Roizman 2001, Vile et al., 1994, to introduce the expression of a nucleotide sequences encoding a cytokine for gene therapy, and said HSV vector comprises an essential gene product under the control of the tumor specific promoters of nestin or bFGF, or EGF, by the teaching of Wright or McKay et al., becasue the HSV vector being non-pathogenic and specifically infect tumor cells without harming healthy cells, and the exogenous nucleotide sequence encoding cytokine is expressed only in the tumor cells, as an essential viral gene product is expressed in a tumor specific manner.

There would have been a reasonable expectation of success given (1) the demonstration that the "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, (2) the

demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994, (3) the demonstration of nextin expression in a brain tumor specific manner by the teachings of McKay et al, and the expression of bFGF and EGF in a prostate cancer specific manner by the teachings of Wright.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's Arguments and ***Responses to Applicant's Arguments*** are the same as discussed in the preceding rejection of claims 16, 28, and 29 as being unpatentable over Roizman et al. in view of Vile et al.

Conclusion

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

5. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you

would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632